Food and Chemical Toxicology 122 (2018) S396–S405

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, octyl butyrate, CAS Registry Number 110-39-4

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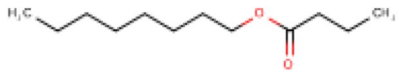
Version: 032218. This version replaces any previous versions.



Name: Octyl butyrate

CAS Registry Number: 110-39-4

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

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https://doi.org/10.1016/j.fct.2018.09.036
Received 17 April 2018; Received in revised form 24 July 2018; Accepted 15 September 2018
Available online 20 September 2018
0278-6915/

DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

Octyl butyrate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hexyl isobutyrate (CAS # 2349-07-7) show that octyl butyrate is not expected to be genotoxic. Data from read-across analog 2-butoxyethyl acetate (CAS # 112-07-2) show that octyl butyrate is not expected to have skin sensitization potential. The repeated dose and developmental endpoints were completed using data from read-across octyl acetate (CAS # 112-14-1), which provided an MOE > 100 for both. The fertility and local respiratory endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; octyl butyrate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic (RIFM, 2003; RIFM, 2014)

Repeated Dose Toxicity: NOAEL = 500 mg/kg/day (Daughtrey et al., 1989a; ECHA Dossier on Octyl acetate)

Reproductive Toxicity: Developmental: NOAEL = 500 mg/kg/day Fertility: No NOAEL available. Exposure is below the TTC (Daughtrey et al., 1989b)

Skin Sensitization: Not a concern for skin sensitization (Kern et al., 2010)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)

Local Respiratory Toxicity: NO NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 301 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 28.35 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h algae EC50: 0.264 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h algae EC50: 0.264 mg/L (US EPA, 2012b)
RIFM PNEC is: 0.0264 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1

1. Identification

1. **Chemical Name:** Octyl butyrate
2. **CAS Registry Number:** 110-39-4
3. **Synonyms:** Butanoic acid, octyl ester; Octyl butanoate; Butyric acid, octyl ester; n-Octyl butyrate; Caprylyl butyrate; 脂肪酸(C = 4 ~ 10)アルキル(又はアルケニル) (C = 8 ~ 24); Octyl butyrate
4. **Molecular Formula:** $C_{12}H_{24}O_2$
5. **Molecular Weight:** 200.32
6. **RIFM Number:** 6115
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 247.73 °C (US EPA, 2012a)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** 4.79 (US EPA, 2012a)
4. **Melting Point:** 12.58 °C (US EPA, 2012a)
5. **Water Solubility:** 3.517 mg/L (US EPA, 2012a)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0221 mm Hg @ 20 °C (US EPA, 2012a), 0.0348 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0018% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.0000090 mg/kg/day or 0.00065 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.000067 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected
   a. **Genotoxicity:** Hexyl isobutyrate (CAS # 2349-07-7)
   b. **Repeated Dose Toxicity:** Octyl acetate (CAS # 112-14-1)
   c. **Reproductive Toxicity:** Octyl acetate (CAS # 112-14-1)
   d. **Skin Sensitization:** 2-Butoxyethyl acetate (CAS # 112-07-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. Natural occurrence (discrete chemical) or composition (NCS)

Octyl butyrate is reported to occur in the following foods by the VCF*:

Apple fresh (*Malus* species)	Mountain papaya (*C. candamarcensis, C. pubescens*)
Babaco fruit (*Carica pentagona* Heilborn)	Okra (*Hibiscus esculentus* L.)
Beer	Passion fruit (*Passiflora* species)
Citrus fruits	Plum (*Prunus* species)
Mangifera species	Strawberry (*Fragaria* species)
Melon	

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 03/14/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, octyl butyrate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Octyl butyrate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of octyl butyrate; however, read-across can be made to hexyl isobutyrate (CAS # 2349-07-7; see Section 5). The mutagenic activity of hexyl isobutyrate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with hexyl isobutyrate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2003). Under the conditions of the study, hexyl isobutyrate was not mutagenic in the Ames test, and this can be extended to octyl butyrate.

There are no studies assessing the clastogenic activity of octyl butyrate; however, read-across can be made to hexyl isobutyrate (CAS # 2349-07-7; see Section 5). The clastogenic activity of hexyl isobutyrate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with hexyl isobutyrate in ethanol at concentrations up to 1720 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Hexyl isobutyrate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014). Under the conditions of the study, hexyl isobutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to octyl butyrate.

Based on the data available, hexyl isobutyrate does not present a concern for genotoxic potential and this can be extended to octyl butyrate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/28/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for octyl butyrate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on octyl butyrate. Read-across material octyl acetate (CAS # 112-14-1; see Section 5) has sufficient repeated dose toxicity data. Groups of 20 SD rats/sex/dose were gavaged with octyl acetate 5 days per week for 13 weeks at doses of 0 (distilled water), 100, 500, or 1000 mg/kg/day. At week 13, relative liver weights among mid- and high-dose animals were statistically significantly increased compared to controls. The increase in liver weights was considered to be adaptive due to lack of histopathological evidence (necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration) showing liver cell damage and associated clinical chemistry alterations (Hall et al., 2012). Relative kidney weights among high-dose animals were also statistically significantly increased compared to controls. Gross pathological examinations did not reveal any differences among treated and control group animals. At week 13, microscopic evaluation of the kidneys revealed evidence of mild tubular nephropathy only in the high-dose male rats. The specific findings consisted of an increased incidence of dilated renal tubules (cortical-medullary zone) containing granular casts and regenerative hyperplasia in proximal convoluted tubules. These histopathological findings were not observed in high-dose females or in either sex among mid- and low-dose group animals. Microscopic alterations in the kidneys of high-dose males were consistent with documented changes of α-2μ-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; and Lehman-McKeeman et al., 1990). There were no reports of confirmatory staining during histopathological examinations. Thus, the NOAEL was considered to be 500 mg/kg/day based on the increased kidney weight among high-dose females (Daughtrey et al., 1989a; also available in ECHA Dossier: Octyl acetate). Therefore, the octyl butyrate MOE for the repeated dose toxicity endpoint can be calculated by dividing the octyl acetate NOAEL in mg/kg/day by the total systemic exposure to octyl butyrate, 500/0.000067 or 7462687.

In addition, the total systemic exposure to octyl butyrate (0.067 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/16/17.

10.1.3. Reproductive toxicity

The margin of exposure for octyl butyrate is adequate for the developmental toxicity endpoint at the current level of use. There are insufficient fertility data on octyl butyrate or on any read-across materials. The total systemic exposure to octyl butyrate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are insufficient developmental toxicity data on octyl butyrate. Read-across material octyl acetate (CAS # 112-14-1; see Section 5) has sufficient developmental toxicity data. A gavage developmental toxicity study was conducted in Sprague Dawley rats. Groups of 22 mated females/sex/group were gavaged on gestation days (GDs) 6–15 with octyl acetate at doses of 0, 100, 500, or 1000 mg/kg neat. Mortality was reported among 2 females from the high-dose group that expired on GD 10 and 12. Maternal animals in the high-dose group had increased incidence of alopecia, rales, red nasal discharge, and anal-genital staining. Additionally, mean body weights were decreased in high-dose treated maternal rats at GDs 9, 12, 16, and 20 when compared to the control group. Four fetuses from the high-dose group had different types of vertebral anomalies in the form of incomplete ossifications, but these were not statistically significantly different compared to controls. Visceral examination revealed dilated lateral cerebral ventricles in 2 fetuses in the high-dose group. These anatomical variations were within the historical controls and thus not considered to be toxicologically relevant. Various types of skeletal variations of incomplete ossifications were observed in all groups. The total number of fetuses (litters) with malformations in the control, low-dose, mid-dose, and high-dose groups were 1(1), 1(1), 1(1), and 6(6), respectively. Thus, the NOAEL for maternal toxicity was considered to be 500 mg/kg/day, based on incidences of clinical observations and decrease in body weights among high-dose group females. The authors of the study determined the developmental toxicity NOAEL to be 1000 mg/kg/day (Daughtrey et al., 1989b). Since there were anomalies observed in fetuses of the highest dose group, a more conservative NOAEL of 500 mg/kg/day was considered for the developmental toxicity endpoint. Therefore, the octyl butyrate MOE

for the developmental toxicity endpoint can be calculated by dividing the octyl acetate NOAEL in mg/kg/day by the total systemic exposure to octyl butyrate, 500/0.000067or 7462687.

There are no fertility data on octyl butyrate or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to octyl butyrate (0.067 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/16/17.

10.1.4. Skin sensitization

Based on the read-across material 2-butoxyethyl acetate (CAS # 112-07-2), octyl butyrate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. There are Insufficient skin sensitization studies for octyl butyrate. Based on the read-across analog 2-butoxyethyl acetate (CAS # 112-07-2; see Section 5), octyl butyrate does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). Read-across analog 2-butoxyethyl acetate was found to be negative in the *in vitro* KeratinoSens, U937-CD86, and human Cell Line Activation Test (h-CLAT) tests, but positive in a direct peptide reactivity assay (DPRA) (Natsch et al., 2013; Otsubo et al., 2017). However, in a murine local lymph node assay (LLNA), read-across analog 2-butoxyethyl acetate was found to be negative up to the maximum tested concentration of 50%, which resulted in a Stimulation Index (SI) of 1.2 (Kern et al., 2010). In guinea pigs, a Buehler test did not present reactions indicative of sensitization for the read-across material 2-butoxyethyl acetate (ECHA dossier: 2-butoxyethyl acetate, accessed 7/25/17). Based on weight of evidence from the read-across analog 2-butoxyethyl acetate, octyl butyrate does not present a concern for skin sensitization.

Additional References: Roberts et al., 2007

Literature Search and Risk Assessment Completed On: 7/25/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, octyl butyrate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for octyl butyrate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009, 2009). Based on lack of absorbance, octyl butyrate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, $1000\,L\,mol^{-1}\cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/12/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for octyl butyrate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on octyl butyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.00065 mg/day. This exposure is 2154 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/09/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of octyl butyrate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in RIFM (2002. In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, octyl butyrate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify octyl butyrate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), octyl butyrate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Octyl butyrate has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

	(mg/L)	(*Daphnia*) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level **(Tier 1)**	0.9901			1,000,000	0.0009901	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.626	0.965	0.264	10,000	0.0264	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.510	0.375	0.81			Neutral Organic

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002).

Exposure	Europe	North America
Log K_{ow} used	4.8	4.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.0264 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/1/2017.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.09.036.

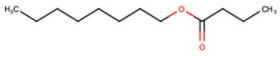
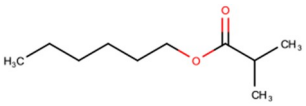
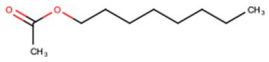
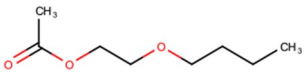
Appendix

Read-across justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Octyl butyrate	Hexyl isobutyrate	Octyl acetate	2-Butoxyethyl acetate
CAS No.	110-39-4	2349-07-7	112-14-1	112-07-2
Structure				
Similarity (Tanimoto Score)		0.82	0.93	0.57
Read-across Endpoint		• Genotoxicity	• Repeated Dose toxicity • Developmental toxicity	Skin sensitization
Molecular Formula	$C_{12}H_{24}O_2$	$C_{10}H_{20}O_2$	$C_{10}H_{20}O_2$	$C_8H_{16}O_3$
Molecular Weight	200.32	172.27	172.27	160.21
Melting Point (°C, EPI Suite)	12.58	−20.47	−9.50	−15.23
Boiling Point (°C, EPI Suite)	247.73	198.83	210.70	191.62
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.64	51	29.1	71.5
Log Kow (KOWWIN v1.68 in EPI Suite)	4.79	3.74	3.81	1.57
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.517	38.59	33.39	3103
J_{max} (mg/cm^2/h, SAM)	8.707	61.193	33.5	26.22
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.28E+002	1.29E+002	1.29E+002	6.46E-001
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found		
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found		
Carcinogenicity (ISS)	• Non-carcinogen (low reliability) • No alert found	• Non-carcinogen (low reliability) • No alert found		

DNA Binding (Ames, MN, CA, OASIS v1.1)				
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found		
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified		
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	
Developmental Toxicity				
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, non-cyclic structure		• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (moderate reliability)		• Non-toxicant (low reliability)	
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found			• No alert found
Protein Binding (OECD)	• No alert found			• No alert found
Protein Binding Potency	• Not possible to classify			• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found			• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found			• No alert found
Local Respiratory Toxicity				
Respiratory Sensitization (OECD QSAR Toolbox v3.4)	• No alert found			
Metabolites				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on octyl butyrate (CAS # 110-39-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, hexyl isobutyrate (CAS # 2349-07-7), octyl acetate (CAS # 112-14-1), and 2-butoxyethyl acetate (CAS # 112-07-2), were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Hexyl isobutyrate (CAS # 2349-07-7) was used as a read-across analog for the target material octyl butyrate (CAS # 110-39-4) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a straight chain primary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a butyrate fragment and the read-across analog has an isobutyrate fragment. Also, the target substance has a C8 alcohol fragment and the read-across analog has a C6 alcohol fragment. These structural differences are toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the straight chain primary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target substance and $\leq \%80$ for the read-across analog. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v3.4, the structural alerts for the toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Octyl acetate (CAS # 112-14-1) was used as a read-across analog for the target material octyl butyrate (CAS # 110-39-4) for the repeated dose and developmental endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a straight chain primary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a butyrate fragment and the read-across analog has an acetyl fragment. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the straight chain primary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-butoxyethyl acetate (CAS # 112-07-2) was used as a read-across analog for the target material octyl butyrate (CAS # 110-39-4) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a straight chain primary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a C8 alcohol fragment and the read-across analog has a C7 alcohol fragment. The read-across analog has an additional inert ether linkage in the alcohol fragment. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the straight chain primary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target substance and $\leq \%80$ for the read-across analog. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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